Depressive symptoms at old age : proactive management in general practice

Weele, G.M.

Chapter 6

Effects of a stepped-care intervention program among older subjects who screened positive for depressive symptoms in general practice: the PROMODE randomized controlled trial

GM van der Weele, MWM de Waal, WB van den Hout, AJM de Craen, Ph Spinhoven, T Stijnen, WJJ Assendelft, RC van der Mast, J Gussekloo

Submitted

ABSTRACT

Objectives To determine (cost-)effectiveness of a stepped-care intervention program among subjects ≥ 75 years who screened positive for depressive symptoms in general practice.
Design pragmatic cluster-randomized controlled trial with 12-months follow-up and primary outcome at 6 months.
Setting 67 Dutch general practices.
Subjects 239 subjects ≥ 75 years who screened positive for untreated depressive symptoms (15-item Geriatric Depression Scale score ≥ 5 points).
Methods Usual care (34 practices with 118 subjects) was compared with stepped-care intervention (33 practices with 121 subjects) consisting of 3 steps: individual counseling; the Coping with Depression course; and - if indicated - referral back to GP to discuss further treatment. Measurements included severity of depressive symptoms (Montgomery-Åsberg Depression Rating Scale; MADRS), quality of life, mortality and costs.
Results At 6 months MADRS-scores had improved more in the usual care than in the intervention group (-2.9 versus -1.1 points, p=0.032), but not at 12 months (-3.1 versus -4.6, p=0.084). No significant differences were found within two separate age groups (75-79 years and ≥ 80 years). In intervention practices, of 121 screen-positive subjects 101 (83%) accepted referral to the stepped-care program. Course participation was accepted only by 23 (19%) subjects.
Conclusions Among older subjects who screened positive for depressive symptoms, an offered stepped-care intervention program was not (cost-)effective compared with usual care, possibly due to a low uptake of the course-offer.

Trial registration: www.controlled-trials.com/ISRCTN 71142851

INTRODUCTION

Depressive symptoms at old age have a negative impact on wellbeing,[1;2] quality of life,[3] daily functioning and mortality,[4] and increase the risk of developing major depression.[5] At old age depressive symptoms are reported to be under-recognized and undertreated,[6] although psychological interventions have shown positive effects on clinical outcomes.[7;8] Therefore, screening older subjects for depressive symptoms, followed by effective treatment of screen-positive subjects is advocated.[6] Two large randomized controlled trials (RCTs) in the USA evaluated the (cost-)effectiveness of care management programs for depressed subjects ≥ 60 years, who were (partly) detected by screening, and showed reduced suicidal ideation,[9] reduced depressive symptoms[10] and cost-effectiveness.[11] However, it is unknown whether screening for depressive symptoms followed by an intervention offer is beneficial and cost-effective for the oldest old. Therefore, the PROMODE study (Proactive Management of Depression in the Elderly) was initiated. PROMODE consisted of a screening study[12] and a subsequent pragmatic RCT offering either a stepped-care intervention or usual care.
The aim of the present study was to investigate the effects and costs of the stepped-care intervention offered to subjects ≥ 75 years who were screened positive for untreated depressive symptoms, compared with usual care. Subjects aged 75-79 years and ≥ 80 years were also examined separately, to reveal possible age-dependent differences in the effect of this program.

METHODS

Study procedures and population

From April 2007 until July 2008, in 67 general practices in the Leiden region (the Netherlands) all 11,635 registered subjects aged ≥ 75 years were invited for screening at home for depressive symptoms. Exclusion criteria were current treatment for depression, clinical diagnosis of dementia or a Mini-Mental State Examination (MMSE) score < 19 points, loss of partner or child in the preceding 3 months, life expectancy ≤ 3 months, and not speaking Dutch. Screening procedures have been described previously.[12]
Screening yielded 264 screen-positive subjects according to a ≥ 5 points score on an interviewer-administered 15-item version of the Geriatric Depression Scale (GDS-15).[13] Of those, 239 subjects gave written informed consent to participate in the randomized trial. The Medical Ethical Committee of the Leiden University Medical Center approved the study.

Intervention and usual care

General practitioners (GPs) in intervention practices were instructed to inform screen-positive subjects about the screening result and to motivate them for referral to the community mental health centre. Subsequent stepped-care intervention consisted of: Step 1 - individual counseling concerning treatment needs and motivation of the subjects during one or two home-visits by a community psychiatric nurse; Step 2 - the Coping with Depression course by trained mental health professionals; if indicated (irrespective of course participation), step 3- referral back to GP to discuss further treatment.
The 'Coping with Depression' course, based on cognitive behavioral therapy, is effective in treating older subjects with depressive symptoms.[14] It consists of 10 weekly group meetings, with 2 course instructors and about 6-10 participants. If subjects were willing to accept the course offer, but had problems with attending group sessions, the course was offered on an individual basis at their home.

To ensure usual care, GPs in control practices were not informed about screen-positive subjects in their practice before the end of the study. Only in case of severe depressive symptoms (MADRS-score > 30 points, see Measurements) and/or suicidal ideation was the GP contacted by the researcher. Patients in the control practices were not individually informed about being screen-positive and treatment allocation.

Randomization and blinding

A cluster randomized design, with the general practice as unit of randomization, was chosen to prevent contamination.[15] After completion of screening and baseline assessment, block randomization was performed using opaque envelopes. Research nurses were not informed about practice allocation.

Measurements

The GDS-15 was used as screening tool for depression. To measure cognitive functioning the MMSE was used.[16] Subjects with an MMSE-score < 19 points were excluded because of reduced reliability and validity to fill out the other questionnaires.

Primary outcome measure was change in severity of depressive symptoms between study groups after 6 months as assessed with the Montgomery Åsberg Depression Rating Scale (MADRS).[17] The MADRS scale consists of 10 items representing the depression core symptoms. For each item, scores range from 0 to 6 points, with higher scores indicating more serious depression. Training of nurses occurred on a regular basis, with special attention paid to administering and scoring the MADRS in a uniform way. Therefore, the MADRS part of the interviews was videotaped; all MADRS scales were scored by both the interviewer and another research nurse, and consensus scores were used in the analyses.

Secondary outcome measures were change in MADRS-score between study groups after 12 months; percentage responders to treatment (intervention or usual care) defined as ≥ 50% decrease in MADRS-score compared to baseline at 6 and 12 months; quality of life, mortality and costs. For further measurements see Appendices 1 and 3.

Follow-up

At 6 and 12 months after baseline measurements, subjects were visited at home to assess the GDS-15, MADRS, SF-36, chronic pain and MMSE (only at 12 months).

Sample size calculation

It was assumed that each cluster would provide 3 screen-positive subjects, on average 1.5 subjects per age group. We planned to include 33 clusters per study arm to detect a clinically relevant difference in MADRS-score of at least 6 points in each age group (assumptions: sd=10 points, power 80%, α=0.05, Intracluster Correlation Coefficient (ICC) = 0.2).

Statistical analysis

Analyses were performed for all subjects and for both age groups separately. MADRS-score changes after 6 and 12 months were analysed according to an intention-to-treat basis. First, we analysed outcomes on the subject level. Sensitivity analyses were performed by substituting missing MADRS-score data at 6 and 12 months following 3 methods: 1) last-observation-carried-forward (LOCF), 2) highest MADRS-scores in our study (30 points at 6 months and 29 points at 12 months), and 3) lowest MADRS-score in our study (0 points at 6 months and 12 months).

Second, MADRS data were analysed using Linear Mixed Models (LMM) to account for clustering at practice level, with adjustment for MADRS-scores at baseline, age and gender. Finally, measurements at 12 months were also included in the model to analyse the long-term effect.

To check whether subgroups benefited from the intervention on the longer term, stratified analyses were performed using LMM with the outcome MADRS-score changes at 12 months dependent on the presence of DSM-IV-diagnosis of depressive disorder, perceived loneliness, chronic diseases, treatment per protocol, and baseline MADRS-score > 10 points.

Hazard ratios (HR) for death were estimated using a Cox proportional hazards model. Statistical analyses were carried out using the SPSS 16.0 for Windows.

RESULTS

Study population

After baseline measurements, 33 practices with 121 subjects were randomly allocated to the intervention arm and 34 practices with 118 subjects to the control arm (Figure 1). The researcher contacted the GP for 3 subjects in control practices and for 2 subjects in intervention practices because of a MADRS-score > 30 points and/or suicidal ideation. In the intervention group 7 subjects died, 10 subjects refused follow-up visits at 6 and/or 12 months, and 3 subjects were unable to reliably answer the questions at 12 months. In the control group 17 subjects died (including one subject who committed suicide, with a MADRS-score < 30 points and no suicidal ideation at baseline), 6 subjects refused follow-up visits at 6 and/or 12 months, and 2 subjects had become incompetent at 12 months. As a result, 210 subjects could be analyzed at 6 months (107 intervention and 103 control subjects), and 194 subjects at 12 months (101 intervention and 93 control subjects).

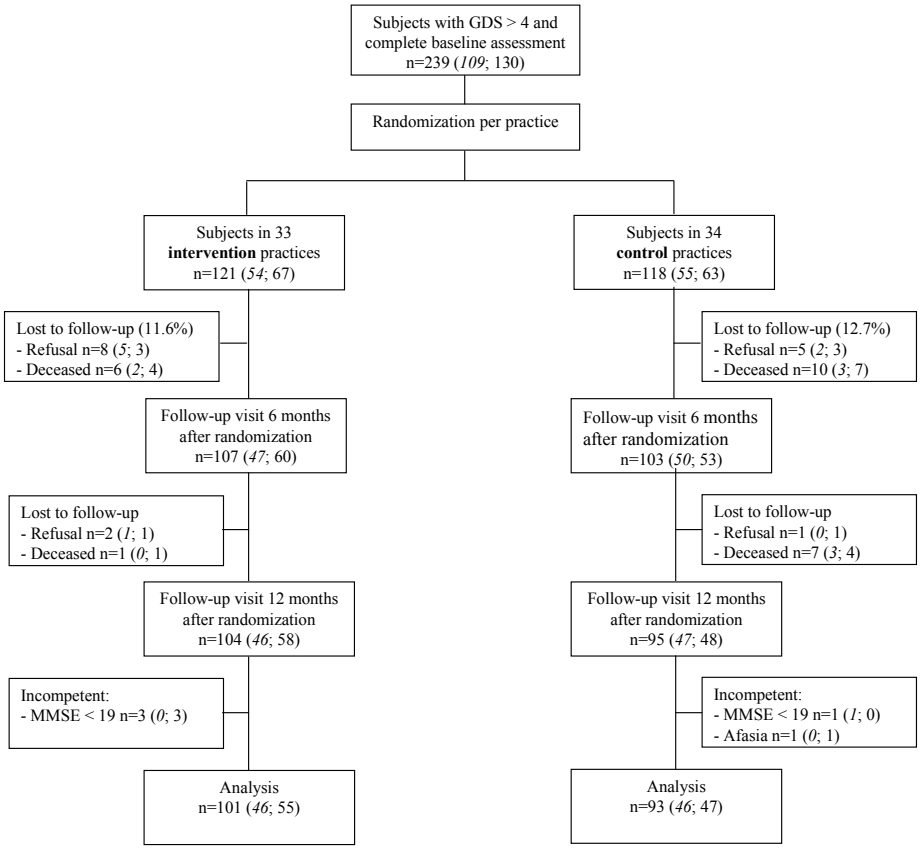

Figure 1: Flow chart of the PROMODE intervention study giving numbers of study subjects per age group between brackets (75-79 years in italics; 80 years and over not italicized)

Table 1 presents the demographic and clinical characteristics at baseline. Baseline characteristics between groups were similar.

Table 1. Baseline characteristics of the study subjects.
Data are presented as numbers and percentages or medians and interquartile ranges

	Intervention group (n=121)		**Control group** (n=118)	
Sociodemographic characteristics				
Age in years	80	(77-84)	80	(77-84)
Female sex	85	(70)	88	(75)
Income social security only	17	(14)	23	(20)
Living alone	76	(63)	78	(66)
Living independently	86	(71)	85	(72)
Clinical characteristics				
Perceived loneliness present	81	(67)	83	(70)
Alcohol intake > 14 drinks/week	10	(8)	13	(11)
Chronic pain present	81	(67)	80	(68)
Somatic co-morbidity (CIRS-TSC)	13	(9-16)	13	(10-17)
SF-36 Physical component score	45	(38-52)	44	(38-53)
SF-36 Mental component score	46	(40-52)	46	(40-51)
Neuropsychiatric characteristics				
MADRS score	12	(8-18)	14	(11-17)
GDS-15 score	6	(5-8)	7	(6-9)
DSM-IV diagnosis present	52	(43)	53	(45)
Major depression present	17	(14)	19	(16)
Minor depression present	16	(13)	12	(10)
Dysthymia present	19	(16)	22	(19)
HADS-A score	5	(3-6)	5	(3-8)
MMSE score	28	(26-29)	28	(26-29)

CIRS-TSC=Cumulative Illness Rating Scale total score; MADRS= Montgomery-Åsberg Depression Rating Scale; GDS-15=Geriatric Depression Scale 15-items version; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders (4th edition); HADS-A= Hospital anxiety depression Scale, anxiety-subscale; MMSE=Mini-Mental State Examination; SF-36=Short-Form 36 items

Intervention uptake

In the intervention practices, 101 of all 121 screen-positive subjects (83%) accepted referral to the community mental health centre to start with the stepped-care intervention. Course participation was accepted by 23 (19%) subjects, of whom 16 (70%) finished the course. Additionally, two subjects followed the course on an individual basis and 21 participated in a group course. Five other subjects (4%) started another type of treatment.

Severity of depressive symptoms during follow-up

During follow-up, there was an overall decrease in MADRS-scores, meaning an improvement in severity of depressive symptoms. After 6 months this decrease was significantly stronger in the control group than in the intervention group, but not after 12 months (Table 2). Sensitivity analyses, after substitution of missing data by LOCF or by the highest or lowest MADRS-scores in our study population, did not substantially change these results (data not shown).

Taking clustering of subjects into account, and controlling for baseline MADRS-score, age and gender, the decrease in MADRS-score after 6 months was 1.4 points less in the intervention group than in the control group (p=0.056, ICC=0). Including measurements at 12 months, MADRS-scores in the intervention group tended to be higher at all measurement moments (p=0.088, ICC=0.045). In none of the analyzed subgroups a positive intervention effect was observed (data not shown).

Table 2. MADRS outcomes at 6 months and 12 months in the intervention and control group.

	Intervention (n=121)		**Control** (n=118)		**p-value**
MADRS scores at 6 months					
Subjects, n	107		103		
MADRS-score, median (IQR)	12	(7-16)	11	(6-15)	0.22
MADRS responders, n (%)	17	(16)	23	(22)	0.24
MADRS-change compared to baseline, mean (sem)	-1.1	(0.61)	-2.9	(0.58)	0.032
MADRS scores at 12 months					
Subjects, n	101		93		
MADRS-score, median (IQR)	10	(6-14)	10	(5-13)	0.45
MADRS responders, n (%)	21	(21)	31	(33)	0.049
MADRS-change compared to baseline, mean (sem)	-3.1	(0.61)	-4.6	(0.64)	0.084

MADRS= Montgomery-Åsberg Depression Rating Scale; IQR=Inter Quartile Range; sem=standard error of the mean; Responder=subject with MADRS score-decrease ≥ 50% compared to baseline.
Continuous data are compared with the Mann-Whitney U test, categorical data with the Chi-square test, and changes of means with independent samples t-test.

Mortality
A total of 24 subjects died during follow-up, 7 (5.8%) in the intervention group and 17 (14.4%) in the control group (HR 2.7; 95% CI 1.1-6.5, adjusted for age and gender). After further adjustment for baseline MADRS-score and co-morbidity (CIRS-total score) HR was 2.3 (95% CI 0.94-5.6).

Age-stratified results
Between subjects aged 75-79 years and ≥80 years no differences were found in course participation and finishing the course. In both age groups, the intervention showed no positive effects on any of the MADRS-outcomes or mortality (see Appendix 2).

Economic evaluation
Costs of the stepped-care intervention were estimated at €333 per referral to the stepped-care program (n=101). No significant differences were found in other costs or quality of life (see Appendix 3).

DISCUSSION

The present study shows no beneficial effect regarding severity of depressive symptoms of a stepped-care intervention program among subjects aged ≥ 75 years who screened positive for untreated depressive symptoms, which were mostly mild to moderate, in general practice. Without beneficial effect, also the cost-effectiveness of the program is unfavorable.

These negative findings are in contrast with the mainly positive reviews reporting that screening or case finding with subsequent enhanced care is effective in decreasing symptoms of depression[18-20] albeit sometimes marginally.[21] However, compared to the present study, most studies included in these reviews targeted their intervention at populations with more (serious) depressive symptoms and/or were performed in younger populations (mostly from 55 or 60 years). Furthermore, studied interventions are heterogeneous and 'usual care' may have relevant cross-cultural differences. In the Dutch healthcare system, GPs are the primary caregivers for all community-living subjects and often have a longstanding and close relationship with their registered (older) patients. This enables a continuity of care that probably resembles the idea of a 'personal care manager', a seemingly important factor in successful interventions such as IMPACT.[9] Our aim was to enhance primary care in the intervention-arm. However, we suspect the marginal role of the GP gave a breach in continuity of care that was not beneficial. A recent Dutch trial (comparable with our study regarding healthcare setting, age group and severity of depressive symptoms) did find a significant intervention effect of stepped care on risk

reduction of developing a major depressive or anxiety disorder.[8] Our negative results are in line with a recent meta-analysis that concluded that psychological treatment for depressive symptoms is effective in primary care, but only when patients were referred by their GP for treatment and not when they were detected by screening.[22]

Our study has some major strengths. Firstly, we did not only focus on older persons with major depression and/or dysthymia but we focused on subjects who screened positive for clinically relevant depressive symptoms, which represents the full spectrum of depression seen in general practice. This is especially important at old age, given the relatively high prevalence of subthreshold and minor depression, thereby enhancing the generalizability of our results in general practice. For the same reason we chose a pragmatic study design, not strongly regulating the process of the intervention carried out by mental healthcare.[23] Secondly, our study was powered to investigate effects in two separate age groups, 75-79 years and ≥ 80 years. Mortality risk was higher in the control group than in the intervention group (if the age groups are combined) but not in the age-stratified groups, suggesting that our study may have been underpowered to draw definite conclusions per age group for mortality.

A possible limitation of the present study is that we chose a change in MADRS-score as our primary outcome measure. Although the MADRS is frequently used and validated to measure (changes in) severity of depressive symptoms among older subjects with moderate to severe depression, it may not be the optimal instrument to measure change in relatively mild depressive symptoms, and is not validated as such. Furthermore, our study could not be blinded and control subjects could have been triggered to seek help. This attention bias[24] may have played a role in our study, since the control group appeared to have received some more psychological care, which may have led to an underestimation of the treatment effect. Also, the research nurses could not be completely blinded for treatment allocation during follow-up visits, although they were not informed about this by the research team. To avoid a biased assessment and scoring of the MADRS, permanent training for the research nurses was provided and all videotaped MADRS interviews were independently scored.

Our study shows a low uptake (19%) of the course-offer among screen-positive older subjects, which probably is not surprising since these subjects did not (have the intention to) ask for help. In a qualitative exploration we found that important reasons for declining the course offer were: not feeling depressed, or having negative thoughts about the course effect, about group participation, or about being too old to change and learn new things.[25] Being screen-positive requires further exploration of subjective complaints and needs, as well as the motivation to accept help. Moreover, particularly in old age, it seems important that exploration of needs should not only focus on the depressive symptoms but also on

other domains, such as functional limitations and chronic pain. Such an exploration will probably require a longitudinal approach with several stages and a broad scope with respect to possible intervention options. Furthermore, in the present study the GPs (who are a respected and trusted advisor for most elderly subjects) were allocated only a limited role, because we assumed that they could not invest the extra time required for the follow-up of screen-positive subjects. It is an important question whether an intervention program would have been more successful if the GP had been more involved in exploring their patients' needs after screening.

In conclusion, among older subjects who screened positive for depressive symptoms in general practice the offer of a stepped-care intervention did not result in better clinical outcomes compared with usual care. Possibly, this was partly due to the low uptake of the main part of the intervention. Therefore, this combined screening/stepped-care intervention program for depressive symptoms does not seem to be a useful strategy to deal with untreated depressive symptoms at old age. It seems worthwhile to explore whether a more individualized approach for screen-positive subjects would yield more effective results.

KEY POINTS

- Stepped-care intervention program for screen-positive depressed subjects aged 75 years and over did not result in better clinical outcomes compared with usual care.
- Among screen-positive subjects the uptake of the main part of the intervention was only 19%.
- Economic evaluation of the stepped-care intervention program also showed no favorable results.

ACKNOWLEDGEMENTS

The study was funded by a grant from the Netherlands Organisation for Health Research and Development (ZonMw) and a grant from Rivierduinen, Center for mental health care. The funders had no role in the study design, collection, analysis and interpretation of data. We thank all subjects, GPs and research nurses (Astrid Cock, Els de Haas and Inge Mooyekind) who contributed to this research project.

REFERENCES

1. Beekman AT, Penninx BW, Deeg DJ, de Beurs E, Geerling SW, van Tilburg W. The impact of depression on the well-being, disability and use of services in older adults: a longitudinal perspective. *Acta Psychiatr Scand* 2002;105(1):20-7.

2. Lyness JM, Kim J, Tang W, et al. The clinical significance of subsyndromal depression in older primary care patients. *Am J Geriatr Psychiatry* 2007;15(3):214-23.

3. Unutzer J, Patrick DL, Diehr P, Simon G, Grembowski D, Katon W. Quality adjusted life years in older adults with depressive symptoms and chronic medical disorders. *Int Psychogeriatr* 2000;12(1):15-33.

4. Penninx BW, Geerlings SW, Deeg DJ, van Eijk JT, van Tilburg W, Beekman AT. Minor and major depression and the risk of death in older persons. *Arch Gen Psychiatry* 1999; 56(10):889-95.

5. Cuijpers P, Smit F. Subthreshold depression as a risk indicator for major depressive disorder: a systematic review of prospective studies. *Acta Psychiatr Scand* 2004;109(5):325-31.

6. Pignone MP, Gaynes BN, Rushton JL, et al. Screening for depression in adults: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002 21; 136(10):765-76.

7. Cuijpers P, Smit F, van Straten A. Psychological treatments of subthreshold depression: a meta-analytic review. *Acta Psychiatr Scand* 2007;115(6):434-41.

8. van't Veer-Tazelaar PJ, van Marwijk HW, van Oppen P, et al. Stepped-care prevention of anxiety and depression in late life: a randomized controlled trial. *Arch Gen Psychiatry* 2009; 66(3):297-304.

9. Bruce ML, Ten Have TR, Reynolds CF, III, et al. Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: a randomized controlled trial. *JAMA* 2004; 291(9):1081-91.

10. Unutzer J, Katon W, Callahan CM, et al. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. *JAMA* 2002; 288(22):2836-45.

11. Katon WJ, Schoenbaum M, Fan MY, et al. Cost-effectiveness of improving primary care treatment of late-life depression. *Arch Gen Psychiatry* 2005;62(12):1313-20.

12. van der Weele GM, de Waal MW, van den Hout WB, et al. Yield and costs of direct and stepped screening for depressive symptoms in subjects aged 75 years and over in general practice. *Int J Geriatr Psychiatry* 2011; 26:229-238.

13. de Craen AJ, Heeren TJ, Gussekloo J. Accuracy of the 15-item geriatric depression scale (GDS-15) in a community sample of the oldest old. *Int J Geriatr Psychiatry* 2003;18(1):63-6.

14. Haringsma R, Engels GI, Cuijpers P, Spinhoven P. Effectiveness of the Coping With Depression (CWD) course for older adults provided by the community-based mental health care system in the Netherlands: a randomized controlled field trial. *Int Psychogeriatr* 2006; 18(2):307-25.

15. Smelt AF, van der Weele GM, Blom JW, Gussekloo J, Assendelft WJ. How usual is usual care in pragmatic intervention studies in primary care? An overview of recent trials. *Br J Gen Pract* 2010;60(576):e305-e318.

16. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12(3):189-98.

17. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979 Apr;134:382-9.

18. Cuijpers P. Psychological outreach programmes for the depressed elderly: a meta-analysis of effects and dropout. *Int J Geriatr Psychiatry* 1998;13(1):41-8.

19. Van Citters AD, Bartels SJ. A systematic review of the effectiveness of community-based mental health outreach services for older adults. Psychiatr Serv 2004 Nov;55(11):1237-49.

20. Skultety KM, Zeiss A. The treatment of depression in older adults in the primary care setting: an evidence-based review. Health Psychol 2006 Nov;25(6):665-74.

21. Freudenstein U, Jagger C, Arthur A, Donner-Banzhoff N. Treatments for late life depression in primary care--a systematic review. *Fam Pract* 2001;18(3):321-7.

22. Cuijpers P, van Straten A, van Schaik A, Andersson G. Psychological treatment of depression in primary care: a meta-analysis. *Br J Gen Pract* 2009;59(559):e51-e60.

23. Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *CMAJ* 2009;180(10):E47-E57.

24. Sackett DL. Bias in analytic research. *J Chronic Dis* 1979;32(1-2):51-63.

25. van der Weele GM, de Jong R., de Waal MW, et al. Response to an unsolicited intervention offer to persons aged ≥ 75 years after screening positive for depressive symptoms: a qualitative study. *Int Psychogeriatr* 2011;Aug 16: 1-8. [Epub ahead of print]

APPENDIX 1. ADDITIONAL MEASUREMENTS AMONG SUBJECTS WHO SCREENED POSITIVE FOR DEPRESSIVE SYMPTOMS IN THE PROMODE-STUDY

For DSM-IV diagnoses of depression, dysthymia and suicidal ideation, relevant modules of the Mini International Neuropsychiatric Interview (MINI) were used.[1] To measure loneliness, the 6-item version of the De Jong-Gierveld Loneliness Scale was used, > 1 point indicating the presence of perceived loneliness.[2] To measure anxiety the 7-item anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A) was used, with higher scores indicating higher levels of anxiety.[3] Current depression treatment, demographics (marital status, living arrangements, level of income and formal education), alcohol intake, and pain were assessed in a standardized manner. For the general health measure SF-36, scores were converted to a standardized physical component score and mental component score, ranging from 0-100, with higher scores indicating higher levels of wellbeing.[4] Electronic patient records, obtained from the GPs, were used to score the severity of (somatic) morbidity using the Cumulative Illness Rating Scale (CIRS), as another baseline characteristic. Of 14 disease categories, the severity was rated from 0 to 4 according to provided scoring rules and resulting in the CIRS total score (CIRS-TSC).[5]

REFERENCES

1. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59 Suppl 20:22-33.

2. De Jong-Gierveld J, Van Tilburg T. A 6-item scale for overall, emotional and social loneliness; confirmatory test on survey data. *Research on Aging* 2006;28(5):582-98.

3. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med* 1997;27(2):363-70.

4. Ware JE, Jr., Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. *J Clin Epidemio*l 1998;51(11):903-12.

5. Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. *J Am Geriatr Soc* 2008;56(10):1926-31.

APPENDIX 2. AGE STRATIFIED RESULTS OF THE PROMODE-STUDY

The PROMODE-study was designed to investigate the effects (and costs) of the stepped-care intervention offered to subjects ≥ 75 years who were screened positive for untreated depressive symptoms, compared with usual care. Subjects aged 75-79 years and ≥ 80 years were studied separately, in order to reveal any age-dependent differences in the effect of this program (trial registration: www.controlled-trials.com /ISRCTN 71142851). These age-stratified results are presented in this Appendix.

Baseline characteristics

Table A1 presents the demographic and clinical characteristics at baseline for both age groups separately. Within age-groups, baseline characteristics were similar between intervention group and control group.

Intervention uptake

In the intervention practices, 45/54 (83%) screen-positive subjects 75-79 years and 56/67 (84%) screen-positive subjects ≥ 80 years accepted referral to the community mental health centre and were offered the stepped-care intervention. Course participation was accepted by 12/54 (22%) subjects 75-79 years and 11/67 (16%) subjects ≥ 80 years (p=0.42). Of those who participated in the course 9/12 (75%) subjects 75-79 years and 7/11 (64%) subjects ≥80 years finished the course (p=0.55).

Severity of depressive symptoms during follow-up

In both age groups there was an overall decrease (i.e. improvement) in MADRS-scores during follow-up, with no significant differences between treatment groups (Table A2). Sensitivity analyses, after substitution of missing data by LOCF or by the highest or lowest MADRS-scores in our study population, did not substantially change these results (data not shown).

Taking clustering of subjects into account, and controlling for baseline MADRS-score, age and gender, the decrease in MADRS-score after 6 months was similar in both groups; compared with the control group, the decrease in the intervention group was 1.6 points less at age 75-79 years (p=0.12, ICC=0) and 1.2 points less at age ≥ 80 years (p=0.25, ICC=0). Including measurements at 12 months, MADRS-scores in the intervention group tended to be higher at all measurement moments, but no significant differences were found between the two age groups (75-79 years: p=0.36, ICC=0; ≥ 80 years: p=0.12, ICC=0.015). In none of the subgroups that we analyzed a positive effect of the intervention was observed (all p-values > 0.1; data not shown).

Mortality

Stratified for age groups, compared with the intervention group the HR in the control group was 3.1 (95% CI 0.62-15) for participants aged 75-79 years and 2.4 (95% CI 0.83-6.9) for those aged ≥ 80 years. After further adjustment for baseline MADRS-score and co-morbidity (CIRS-total score) the HR was 3.2 (95% CI 0.6-17) for the age group 75-79 years and 1.9 (95% CI 0.61-5.7) for subjects ≥ 80 years.

Table A1. Baseline characteristics of the study subjects aged 75-79 years and ≥ 80 years
(data are presented as numbers and percentages or medians and interquartile ranges)

	Subjects 75-79 years				Subjects ≥ 80 years			
	Intervention group (n=54)		Control group (n=55)		Intervention group (n=67)		Control group (n=63)	
Sociodemographic characteristics								
Age in years	77	(76-78)	77	(76-78)	84	(81-86)	84	(81-87)
Female sex	35	(65)	41	(75)	50	(75)	47	(75)
Income social security only	8	(15)	10	(18)	9	(13)	13	(21)
Living alone	25	(46)	30	(55)	51	(76)	48	(76)
Living independently	43	(80)	48	(87)	43	(64)	37	(59)
Clinical characteristics								
Perceived loneliness present	31	(57)	38	(69)	50	(75)	45	(71)
Alcohol intake > 14 drinks/week	5	(9)	7	(13)	5	(8)	6	(10)
Chronic pain present	32	(59)	38	(69)	49	(73)	42	(67)
Somatic co-morbidity (CIRS-TSC)	14	(8-17)	12	(9-16)	12	(9-16)	13	(11-18)
SF-36 Physical component score	45	(40-52)	45	(38-56)	45	(38-52)	44	(37-50)
SF-36 Mental component score	47	(40-52)	47	(40-52)	45	(39-52)	46	(40-51)
Neuropsychiatric characteristics								
MADRS-score	12	(8-18)	14	(10-18)	12	(8-18)	13	(11-17)
GDS-15 score	6	(5- 8)	7	(6- 9)	7	(5- 8)	7	(5- 9)
DSM-IV diagnosis present	24	(44)	29	(53)	28	(42)	24	(38)
Major depression	10	(19)	8	(15)	7	(10)	11	(18)
Minor depression	7	(13)	11	(20)	9	(13)	1	(2)
Dysthymia	7	(13)	10	(18)	12	(18)	12	(19)
HADS-A score	5	(3- 6)	6	(4- 9)	4	(2- 6)	5	(3- 7)
MMSE score	28	(27-29)	28	(27-29)	28	(26-29)	27	(26-29)

CIRS-TSC=Cumulative Illness Rating Scale total score; MADRS= Montgomery-Åsberg Depression Rating Scale; GDS-15=Geriatric Depression Scale 15-items version; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders (4th edition); HADS-A= Hospital anxiety depression Scale, anxiety-subscale; MMSE=Mini-Mental State Examination; SF-36=Short-Form 36 items

Table A2. MADRS outcomes at 6 and 12 months in the intervention and control groups for the two age groups separately.

	Subjects 75-79 years					Subjects ≥ 80 years				
	Intervention (n=54)		Control (n=55)		p-value	Intervention (n=67)		Control (n=63)		p-value
MADRS-scores at 6 months										
Subjects, n	47		50			60		53		
MADRS-score, median (IQR)	12	(7-16)	10	(7-14)	0.35	13	(8-17)	11	(6-15)	0.45
MADRS responders, n (%)	7	(15)	9	(18)	0.68	10	(17)	14	(26)	0.21
MADRS-change compared to baseline, mean (sem)	-1.2	(0.95)	-3.0	(0.80)	0.15	-0.90	(0.80)	-2.7	(0.84)	0.13
MADRS-scores at 12 months										
Subjects, n	46		46			55		47		
MADRS-score, median (IQR)	9	(5-13)	9	(4-12)	0.96	10	(7-15)	10	(6-14)	0.39
MADRS responders, n (%)	13	(28)	20	(44)	0.13	8	(15)	11	(23)	0.25
MADRS-change compared to baseline, mean (sem)	-4.3	(0.91)	-4.6	(0.76)	0.78	-2.0	(0.81)	-4.6	(1.03)	0.055

MADRS= Montgomery-Åsberg Depression Rating Scale; IQR=Inter Quartile Range; sem=standard error of the mean;
Responder=subject with MADRS-score-decrease ≥ 50% compared to baseline.
Continuous data are compared with the Mann-Whitney U test, categorical data with the Chi-square test, and changes of means with independent samples t-test.

APPENDIX 3 - ECONOMIC EVALUATION OF THE PROMODE-STUDY

AIM

Economic evaluation of a stepped-care intervention program among subjects (aged 75-79 years and ≥ 80 years) who screened positive for depressive symptoms in general practice.

METHODS

Study procedures and population

A total of 239 subjects participated in the PROMODE-study, a pragmatic cluster RCT with an intervention and a 'usual care' control arm. A detailed description can be found elsewhere (chapter 6).

Measurements

To assess health related quality of life for economic evaluations the EuroQol (EQ-5D), a Visual Analogue Scale (VAS) and the Short Form 36 items (SF-36) were measured.[1-3] Costs of intervention and other (in)formal care were calculated. Intervention costs consisted of the individual counseling during one or two home-visits (step 1) and of the group or individual course sessions (step 2), including both health care costs (course instructors, room rental, refreshments, and course materials) and patient costs (time and travel). Voluntary work/activities and use of (in)formal care were assessed in a standardized manner. Electronic patient records, obtained from the GPs, were used to calculate medication costs during the follow-up period.

Follow-up

At 6 and 12 months after baseline measurements, subjects were visited at home to assess the EQ-5D, VAS, SF-36, and (in)formal care in the previous three months. At 3 and 9 months subjects were contacted by telephone to administer the EQ-5D and the VAS and to ask about the use of (in)formal care in the previous 3 months.

Economic evaluation

In a cost-utility analysis incremental societal costs (intervention and other (in)formal care) were compared with incremental quality-adjusted life years (QALYs). A one-year time horizon was used, without discounting. Costs were valued using standard prices.[4] Missing cost and utility data were substituted using LOCF, except for missing data for deceased subjects (substituted by zero) and for missing baseline values (substituted using next-observation-carried-backward). The utility measures were used to calculate QALYs, i.e. the

area under the 1-year utility curve. In the primary cost-utility analysis, QALYs were calculated using the Dutch tariff for the EQ-5D.[5] As secondary analyses, QALYs were calculated using the UK tariff for the EQ-5D,[6] Brazier's SF-6D tariff,[7] and patients' VAS scores with power transformation.[8] Economic data were compared using non-parametric bootstrapping, which was carried out using Stata/IC 11.0 for Windows. Because of the number of comparisons, a reduced significance level of 0.01 was used for the separate cost items in the economic evaluation.

RESULTS

Table A3 shows the QALYs estimates in both age groups and for all four utility measures. There were no differences between the intervention and control groups in the two age groups (all p-values ≥ 0.19). Table A4 presents the age-stratified costs per person for both groups. Mean costs of the stepped-care intervention per person in the age group 75-79 years were €311 (n=54) and in the age group ≥ 80 years €251 (n=67). Overall mean intervention costs per referred person were estimated at €333 (n=101).
However, the costs of course participation were generated by only a minority of the intervention group. The average intervention costs per course participant were €1461; participants attended (on average) 6.2 course sessions.
Apart from the PROMODE-intervention, the control group appeared to have received some more psychological care than the intervention group during the follow-up period mostly due to a small number of subjects receiving large volumes of care (Table A4), which may have attributed to the lack of effect of the studied intervention.
Table A4 also shows that in the age group 75-79 years total societal costs per person tended to be higher for subjects in the intervention group than in the control group (€14024 versus €9352, p=0.10). In the age group ≥ 80 years these costs were similar in the intervention and control group (€16087 versus €16661, p=0.87).

CONCLUSIONS

In the PROMODE-study cost-utility analysis showed no differences between study groups on any of the utility measures. In the younger age group mean total societal costs tended to be higher for subjects in the intervention group, which was not seen in the older age group.

REFERENCES

1. The EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990,16(3):199-208.

2. Ware JE, Jr., Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. *J Clin Epidemiol* 1998, 51(11):903-912.

3. Aaronson NK, Muller M, Cohen PD et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998, 51(11):1055-1068.

4. Oostenbrink JB, Bouwmans CAM, Koopmanschap MA et al. Handleiding voor kostenonderzoek, methoden en richtlijnprijzen voor economische evaluaties in de gezondheidszorg. Geactualiseerde versie 2004. ed. Amstelveen: College voor Zorgverkeringen, 2004.

5. Lamers LM, Stalmeier PF, McDonnell Jet al. [Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff]. *Ned Tijdschr Geneeskd* 2005,149(28):1574-1578.

6. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997, 35(11):1095-1108.

7. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002, 21(2):271-292.

8. Stiggelbout AM, Eijkemans MJ, Kiebert GM et al. The 'utility' of the visual analog scale in medical decision making and technology assessment. Is it an alternative to the time trade-off? *Int J Technol Assess Health Care* 1996, 12(2):291-298.

Table A3. Quality-adjusted life years (QALYs) between baseline and 12 months per person in the intervention and control groups for the two age groups separately.

	Subjects 75-79 years			Subjects ≥ 80 years		
	Intervention (n=54)	**Control** (n=55)	**p-value**	**Intervention** (n=67)	**Control** (n=63)	**p-value**
QALYs between baseline and 12 months						
According to EQ5D-NL	0.463	0.484	0.68	0.419	0.375	0.33
According to EQ5D-UK	0.404	0.429	0.66	0.350	0.303	0.36
According to SF6D	0.624	0.616	0.78	0.588	0.568	0.46
According to VAS	0.737	0.692	0.20	0.688	0.639	0.19

QALYs=quality-adjusted life years; EQ-5D=EuroQol 5 dimensions; SF-36=Short Form 36 items; VAS=Visual Analogue Scale.
Data are compared using non-parametric bootstrapping.

Table A4. Average volume of 1-year healthcare and costs (in euros) per person in the intervention and control groups for the two age groups separately.

		Subjects 75-79 years					Subjects ≥ 80 years				
		Intervention (n=54)		Control (n=55)			Intervention (n=67)		Control (n=63)		
		Volume*	Costs	Volume*	Costs	p-value†	Volume*	Costs	Volume*	Costs	p-value†
Costs of intervention	Individual consultation(s) (step 1)	1.5 (83%)	99	0 (0%)	0	-	1.5 (84%)	99	0 (0%)	0	-
	Course sessions (step 2)	1.5 (22%)	212	0 (0%)	0	-	0.9 (16%)	152	0 (0%)	0	-
Other psychological care	Psychiatrist (% patients)	0 (0%)	0	0.37 (4%)	39	0.24	0.015 (1%)	1.6	0 (0%)	0	0.32
	Psychologist (% patients)	0.02 (2%)	1.7	0.91 (15%)	84	0.10	0.34 (4%)	32	0.92 (5%)	86	0.40
	Psychiatric admission (nights, % patients)	0 (0%)	0	0.55 (2%)	191	0.32	0 (0%)	0	0 (0%)	0	1.00
GP care	Contacts	11	328	12	350	0.54	8.1	245	11	339	0.027
	Medication (prescribed by GP)		1025		809	0.26		740		738	0.98
Specialist care	Other specialist consultations	6.6	560	5.7	477	0.40	3.2	270	4.4	373	0.12
Paramedical care	Physiotherapist	21	812	11	432	0.038	16	626	13	527	0.38
	Other paramedical consultations	0.28	13	1.7	125	0.047	1.8	84	1.6	80	0.87
Institutional admissions	Hospital daycare (days, % patients)	0.78 (17%)	259	0.24 (18%)	79	0.26	0.12 (10%)	40	0.19 (16%)	63	0.25
	Hospital (nights, % patients)	2.3 (24%)	1086	2.6 (31%)	1219	0.66	2.2 (24%)	1026	5.2 (30%)	2439	0.065
	Nursing home (nights, % patients)	1.7 (2%)	385	2.1 (6%)	478	0.77	9.7 (6%)	2205	6.6 (8%)	1516	0.52
	Care home (nights, % patients)	20 (6%)	1906	7 (4%)	681	0.23	34 (16%)	3248	28 (13%)	2639	0.53
Home care	Nursing care (hours)	35	1563	23	1013	0.42	55	2453	70	3154	0.32
	Formal home care (hours)	71	1715	73	1752	0.89	107	2574	94	2251	0.28
	Other paid home care (hours)	25	234	9	87	0.051	33	301	34	313	0.86
	Informal care (hours)	324	2981	257	2367	0.26	192	1766	259	2381	0.28
Unpaid/voluntary work	Unpaid/voluntary work (hours)‡	834	846	1017	-830	0.08	695	224	745	-238	0.50
Total societal costs	Mean costs per person		14024		9352	0.10		16087		16661	0.87

* Mean number of consultations, sessions, visits, days, nights or hours, and percentage of patients
† means of costs are compared using non-parametric bootstrapping ‡ negative costs indicate savings due to above-average hours of unpaid/voluntary work